UNITED STATES DISTRICT COURT
EASTERN DISTRICT OF NEW YORK

KING PHARMACEUTICALS, INC. and JONES PHARMA, INC.,

Plaintiffs,

v.

EON LABS, INC.,

Defendant.

CV 04 5540

Civil Action No.

IRIZARRY, J.
MANN, M.J.

COMPLAINT

Plaintiffs, King Pharmaceuticals, Inc. ("King") and Jones Pharma Inc. ("Jones") (collectively, "the King Plaintiffs"), for their Complaint against Eon Labs, Inc. ("Eon"), allege as follows:

Nature of the Action

1. This is an action for patent infringement arising under the patent laws of the United States, 35 U.S.C. § 100 *et seq.*, including, *inter alia*, §§ 271(a), 271(b), 271(e)(2), 281-283, and 285.

The Parties

2. King is a corporation organized and existing under the laws of the state of Tennessee, and has a principal place of business at 501 Fifth Street, Bristol, Tennessee 37620. King is engaged in the business of acquiring, developing, marketing, and selling pharmaceutical products throughout the world.

3. Jones is a corporation organized and existing under the laws of the state of Delaware, and has a principal place of business at 1945 Craig Road, St. Louis, Missouri 63146. Jones is a wholly owned subsidiary of King.

4. Upon information and belief, Eon is a corporation organized and existing under the laws of the state of Delaware, and has a place of business at 227-15 N. Conduit Avenue, Laurelton, New York 11413. Upon information and belief, Eon is engaged in the business of preparing generic prescription pharmaceuticals for distribution throughout the United States.

Jurisdiction and Venue

5. This Court has jurisdiction over the subject matter of this action pursuant to 28 U.S.C. §§ 1331 and 1338(a).

6. This Court has personal jurisdiction over Eon by virtue of, *inter alia*, Eon's place of business in New York.

7. Venue is proper in this judicial district pursuant to 28 U.S.C. §§ 1391(c) and 1400(b).

The Patents-In-Suit and the SKELAXIN® Drug Product

8. On June 18, 2002, the United States Patent and Trademark Office issued to Elan Pharmaceuticals, Inc. ("Elan") United States Patent No. 6,407,128 ("the '128 patent") (attached hereto as Exhibit 1), entitled "Method for Increasing the Bioavailability of Metaxalone."

9. On June 12, 2003, Elan assigned to Jones all rights, title, and interest in and to the '128 patent, including the right to sue and recover damages or obtain injunctive relief for past, present, and future infringement thereof.

10. On January 27, 2004, the United States Patent and Trademark Office issued to Jones United States Patent No. 6,683,102 ("the '102 patent") (attached hereto as Exhibit 2), entitled "Methods of Using Metaxalone in the Treatment of Musculoskeletal Conditions."

11. The King Plaintiffs market and sell metaxalone in the United States under the brand name SKELAXIN®, which is listed in the United States Food and Drug Administration's

("FDA") *Approved Drug Products With Therapeutic Equivalence Evaluations* (attached hereto as Exhibit 3).

12. The SKELAXIN® product label (attached hereto as Exhibit 4) instructs doctors and patients that the bioavailability of metaxalone may be increased by administering to a patient receiving metaxalone therapy a therapeutically effective amount of metaxalone in a pharmaceutical composition with food.

Count for Infringement of the '128 Patent

13. The King Plaintiffs incorporate by reference the averments of Paragraphs 1-12 as if set forth herein.

14. On or about August 31, 2001, Eon filed Abbreviated New Drug Application ("ANDA") No. 40-445 with the FDA pursuant to § 505(j) of the Federal Food, Drug, and Cosmetic Act, 21 U.S.C. § 355(j), seeking approval to engage in the commercial manufacture, use, sale, or importation of a 400mg generic version of SKELAXIN® in the United States prior to the expiration of the '128 patent.

15. Upon information and belief, Eon amended ANDA No. 40-445 to include an 800 mg strength tablet and relevant bioequivalence information.

16. Upon information and belief, Eon filed with the amended ANDA No. 40-445 a patent certification pursuant to 21 U.S.C. § 355(j)(2)(A)(vii)(IV), commonly known as a "Paragraph IV Certification," alleging that none of the claims of the '128 patent will be infringed by the manufacture, use, or sale of Eon's generic version of SKELAXIN®, and that all of the claims of the '128 patent are invalid.

17. On or about November 3, 2004, King received a letter from Eon purporting to be a Notice of Certification under 21 U.S.C. §§ 355(j)(2)(B)(i) and 355(j)(2)(B)(ii), informing King

of Eon's amended ANDA submission and corresponding certification under 21 U.S.C. § 355(j)(2)(A)(vii)(IV).

18. Pursuant to 35 U.S.C. § 271(e)(2)(A), Eon's submission to the FDA of amended ANDA No. 40-445 to obtain approval to engage in the commercial manufacture, use, or sale of Eon's 800mg generic version of SKELAXIN®, prior to the expiration of the '128 patent, constitutes infringement of the '128 patent.

19. Upon information and belief, amended ANDA No. 40-445 seeks approval of proposed product labeling for Eon's 800mg generic version of SKELAXIN® that is the same, or substantially the same, as the SKELAXIN® labeling.

20. Upon information and belief, pursuant to this labeling, Eon's 800mg generic version of SKELAXIN® will be administered to human patients with food to increase bioavailability, in a therapeutically effective amount for the treatment of musculoskeletal disorders.

21. Pursuant to 35 U.S.C. § 271(b), Eon's commercial manufacture, use and sale of its 800mg generic version of SKELAXIN® will constitute induced infringement of the '128 patent.

22. Upon information and belief, Eon is aware that its generic version of SKELAXIN®, with such labeling, will actively induce, encourage, aid and abet patients and doctors in infringing the '128 patent, and that the sale of such would constitute willful infringement.

Count for Infringement of the '102 Patent

23. The King Plaintiffs incorporate by reference the averments of Paragraphs 1-22 as if set forth herein.

24. Upon information and belief, Eon filed with the amended ANDA No. 40-445 a Paragraph IV Certification alleging that none of the claims of the '102 patent will be infringed by the manufacture, use, or sale of Eon's generic version of SKELAXIN®, and that all of the claims of the '102 patent are invalid.

25. On or about November 3, 2004, King received a letter from Eon purporting to be a Notice of Certification under 21 U.S.C. §§ 355(j)(2)(B)(i) and 355(j)(2)(B)(ii), informing King of Eon's amended ANDA submission and corresponding certification under 21 U.S.C. § 355(j)(2)(A)(vii)(IV).

26. Pursuant to 35 U.S.C. § 271(e)(2)(A), Eon's submission to the FDA of amended ANDA No. 40-445 to obtain approval to engage in the commercial manufacture, use, or sale of Eon's 800mg generic version of SKELAXIN®, prior to the expiration of the '102 patent, constitutes infringement of the '102 patent.

27. Pursuant to 35 U.S.C. § 271(a), Eon's commercial manufacture, use, and sale of its 800mg generic version of SKELAXIN® will constitute direct infringement of the '102 patent.

28. Pursuant to 35 U.S.C. § 271(b), Eon's commercial manufacture, use, and sale of its 800mg generic version of SKELAXIN® will constitute induced infringement of the '102 patent.

29. Upon information and belief, Eon is aware that its 800mg generic version of SKELAXIN®, with such labeling, will directly infringe and actively induce, encourage, aid and abet patients and doctors in infringing the '102 patent, and that the sale of such would constitute willful infringement.

Prayer for Relief

WHEREFORE, the King Plaintiffs demand judgment against Eon as follows:

(a) an injunction against Eon to prevent the commercial manufacture, use, offer to sell, or sale within the United States or importation into the United States of Eon's 800mg generic version of SKELAXIN®;

(b) an order pursuant to 35 U.S.C. § 271(e)(4)(A) that the effective date of any approval of Eon's 800mg generic version of SKELAXIN® will be a date that is not earlier than the date of the expiration of the '128 and '102 patents;

(c) an injunction pursuant to 35 U.S.C. § 271(e)(4)(B) against Eon to prevent the commercial manufacture, use, offer to sell, or sale within the United States or importation into the United States of Eon's 800mg generic version of SKELAXIN®;

(d) damages or other monetary relief pursuant to 35 U.S.C. § 271(e)(4)(C), increased to treble the amount found or assessed, together with interest, if Eon engages in the commercial manufacture, use, offer to sell, or sale within the United States or importation into the United States of Eon's 800mg generic version of SKELAXIN®;

(e) a judgment with respect to amended ANDA No. 40-445 directing Eon to amend its patent certification from a Paragraph IV Certification to a "Paragraph III Certification" pursuant to 21 C.F.R. § 314.94(a)(12)(viii)(A); and

(f) attorneys' fees pursuant to 35 U.S.C. § 285, costs and expenses, and such further and other relief as this Court may deem just and proper.

Respectfully submitted,

Date: December 17, 2004

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EXHIBIT 1

US006407128B1

(12) **United States Patent**
Scaife et al.

(10) **Patent No.: US 6,407,128 B1**
(45) **Date of Patent: Jun. 18, 2002**

(54) **METHOD FOR INCREASING THE BIOAVAILABILITY OF METAXALONE**

(75) Inventors: **Michael Scaife**, Poway; **Jaymin Shah**, Sunnyvale, both of CA (US)

(73) Assignee: **Elan Pharmaceuticals, Inc.**, South San Francisco, CA (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

(21) Appl. No.: **09/998,206**

(22) Filed: **Dec. 3, 2001**

(51) **Int. Cl.**[7] **A61K 31/42**
(52) **U.S. Cl.** **514/376**
(58) **Field of Search** 514/376

(56) **References Cited**

U.S. PATENT DOCUMENTS

3,062,827	A	* 11/1962	Lunsford	260/307
3,993,767	A	11/1976	Alphin et al.	
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5,989,583	A	11/1999	Amselem	
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6,207,178	B1	3/2001	Westesen et al.	
6,265,438	B1	7/2001	Steward	
2001/0024659	A1	9/2001	Chen et al.	

OTHER PUBLICATIONS

Monograph No. 5838 of the Merck Index (11th ed., 1989) for metaxalone.
Lunsford et al., 82 J. Am. Chem. Soc. 1166 (1960).
Skelaxin® monograph, 2001 Physicians' Desk Reference.

* cited by examiner

Primary Examiner—Raymond Henley, III
(74) *Attorney, Agent, or Firm*—Finnegan, Henderson, Farabow, Garrett & Dunner

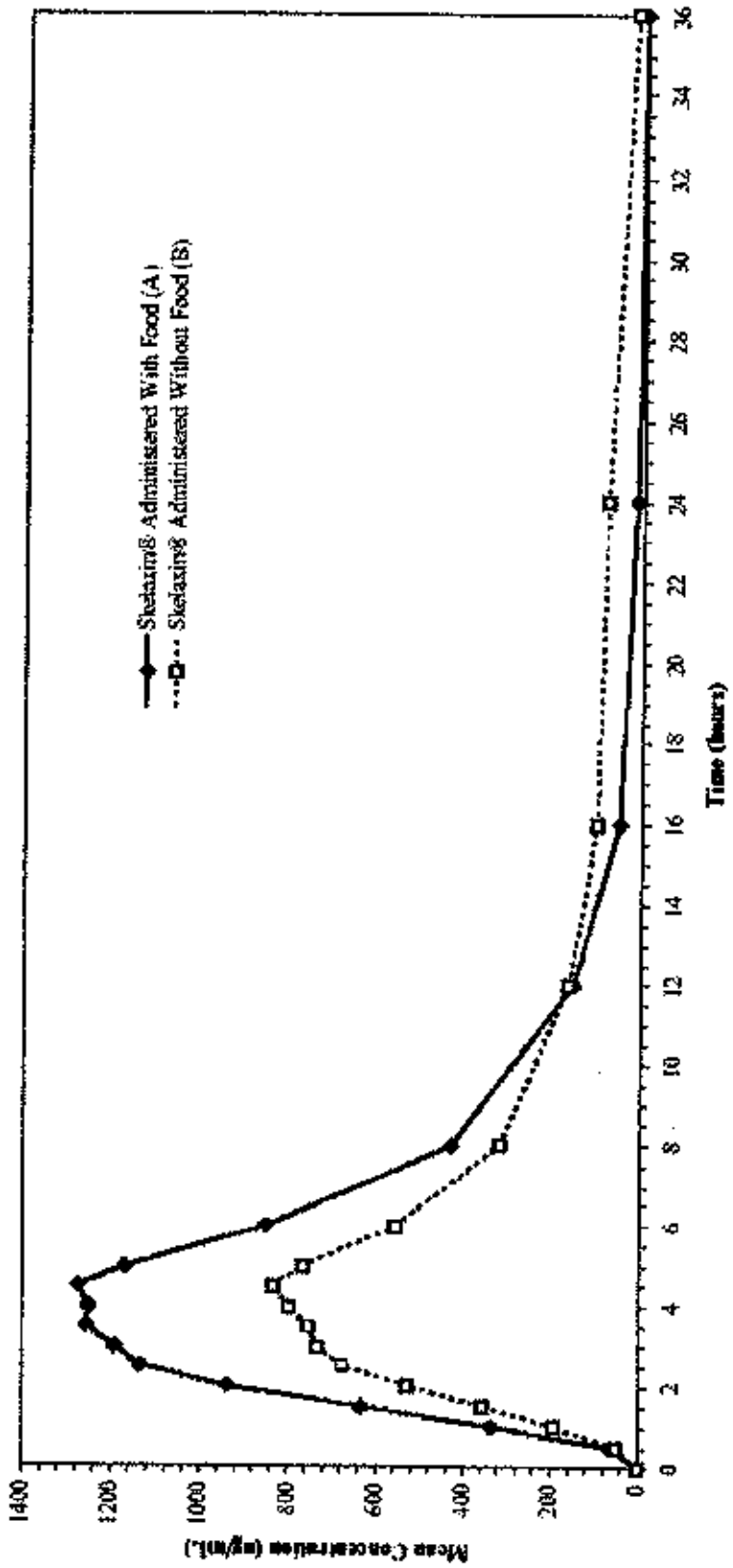
(57) **ABSTRACT**

A method of increasing the bioavailability of metaxalone by administration of an oral dosage form with food is provided, as well as an article of manufacture comprising an oral dosage form of metaxalone in a suitable container and associated with printed labeling which describes the increased bioavailability of the medication in the container when taken with food.

22 Claims, 1 Drawing Sheet

Figure I

Mean Plasma Concentration (0-36 hours)
Number =42



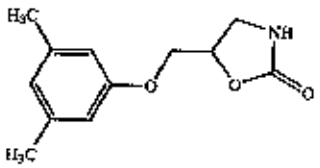
METHOD FOR INCREASING THE BIOAVAILABILITY OF METAXALONE

FIELD OF THE INVENTION

The invention relates to methods for increasing the bioavailability of a medicinal agent, namely metaxalone (5-[(3,5-dimethylphenoxy)methyl]-2 oxazolidinone).

BACKGROUND OF THE INVENTION

Metaxalone (Skelaxin®) has the following chemical structure and name:



5-[(3,5 -dimethylphenoxy)methyl]-2 oxazolidinone

Skelaxin is indicated as an adjunct to rest, physical therapy, and other measures for the relief of discomforts associated with acute, painful musculoskeletal conditions. The mode of action of this drug has not been clearly identified, but may be related to its sedative properties. Metaxalone does not directly relax tense skeletal muscles in man. The commercially available tablet contains: metaxalone, 400 mg along with inert compression tableting excipients.

Metaxalone is further described at Monograph no. 5838 of the Merck Index (Eleventh Addition, Merck & Co., 1989) and is also identified by CAS Registry Number: 1665-48-1. It is also known by the drug code, AHR-438; and the drug product containing it is marketed as Skelaxin® (a trademark of Elan Pharmaceuticals, Inc.).

Preparation of metaxalone is described in Lunsford et al., J. Am. Chem. Soc. 82, 1166 (1960) and U.S. Pat. No. 3,062,827 to Lunsford Nov. 6, 1962 Assignee A. H. Robins), which is incorporated herein in its entirety by reference. The '827 patent discloses the compound and related species as anticonvulsants and antispasmodics, however, these activities have not been borne out by clinical experience.

Metaxalone is a central nervous system depressant that has sedative and skeletal muscle relaxant effects. Metaxalone is indicated as an adjunct to rest, physical therapy and other measures for the relief of discomforts associated with acute, painful musculoskeletal conditions. See Skelaxin® monograph, 2001 Physicians' Desk Reference®, Medical Economics Company, Inc. (publisher) Montvale, N.J.

The most frequent reactions to metaxalone include nausea, vomiting, gastrointestinal upset, drowsiness, dizziness, headache, and nervousness or "irritability." Other adverse reactions are: hypersensitivity reaction, characterized by a light rash with or without pruritus; leukopenia; hemolytic anemia; jaundice.

Pharmacokinetic studies have not previously been conducted to date to evaluate the effect of food on the pharmacokinetics of metaxalone. The hydrophobicity of the metaxalone molecule and the dosage amount required for a therapeutic effect both point to probably limited absorption from the gut when administered orally. More oral bioavailability of the drug substance has been sought to increase both speed of onset and amount of therapeutic effect.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 is a plot of the mean plasma concentration of metaxalone in nanograms per milliliter versus the time elapsed from administration of the dosage form. Two (2) plots are shown for the 400 mg dosage form administered with and without food.

SUMMARY OF THE INVENTION

The subject of this invention is the unexpected finding that administration of metaxalone with food increases both the rate and extent of absorption via the oral dosage form in human subjects.

One aspect of this invention is a method of increasing the bioavailability of metaxalone in a human patient receiving metaxalone therapy wherein the metaxalone is contained in a pharmaceutical composition, which method comprises administering a therapeutically effective amount of metaxalone to the patient with food.

Another aspect of the invention is providing a method of increasing rate and extent of metaxalone absorption as measured by the drug concentration attained in the blood stream over time of a patient receiving, the drug in an oral dosage form which method comprises administering a therapeutically effective amount of metaxalone to the patient with food.

Preferably the therapeutic amount is between about 200 mg to about 900 mg, and more preferably between about 400 mg to about 800 mg. Unit dosage forms are preferred.

Preferably the food is a solid food with sufficient bulk and fat content that it is not rapidly dissolved and absorbed in the stomach. More preferably the food is a meal, such as breakfast, lunch or dinner. Advantageously the dosage is administered to the patient between about 30 minutes prior to about 2 hours after eating a meal, most advantageously the dosage is administered within 15 minutes of eating a meal. The terms "without food", "fasted" and "an empty stomach" are defined to mean the condition of not having consumed solid food for about 1 hour prior to until about 2 hours after such consumption.

Yet another aspect of this invention is providing information to prescribing physicians and patients receiving metaxalone therapy useful in maximizing the therapeutic effect of the oral dosage form, by recommending that metaxalone be taken within about half an hour of consuming food.

Another aspect of this invention is an article of manufacture that comprises a container containing a pharmaceutical composition comprising metaxalone wherein the container holds preferably the metaxalone composition in unit dosage form and is associated with printed labeling instructions advising of the differing absorption when the pharmaceutical composition is taken with and without food.

The effect of food on metaxalone absorption was identified in a study designed to compare the bioavailability of 400 mg of metaxalone in the formulation the drug product Skelaxin® administered to healthy volunteers with and without food.

An objective was to evaluate the bioavailability of metaxalone when administered to subjects with and without food. A single center, single dose, open-label, two-period, randomized, crossover trial in healthy subjects was conducted over a period of approximately 32 days.

The two study drug treatments were as follows:

Treatment A: metaxalone tablet (400 mg) administered with food

Treatment B: metaxalone tablet (400 mg) administered without food

In fed treatment condition A, study drug was taken 15 minutes after th e test meal. The test meal was consumed

over a 15 minute time period. There was a 6-day washout period between study drug administrations. Seventeen blood samples were collected, starting with baseline (0 hour) and at the following time points: 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 6, 8, 12, 16, 24, and 36 hours.

A total of 44 subjects (31 males/13 females) were enrolled and dosed. Only the plasma of subjects who completed the study were assayed and used for the pharmacokinetic analysis.

A single center, single dose, open label, two-period crossover trial was devised for study in healthy subjects. Each administration was a single oral dose of one Skelaxin® 400 mg tablet with or without food. The study drug was administered as follows:

Treatment A: One (1) 400 mg tablet of metaxalone with 240 mL of room temperature water with food: Breakfast was given to the subjects 30 minutes prior to dosing and eaten within a 15 minute period. The dose of study drug was administered to the subjects 15 minutes after the breakfast was finished.

The breakfast consisted of the following:

2 eggs (fried in butter);
2 strips of bacon;
2 slices of toast with butter;
4 ounces of hash brown potatoes;
1 glass whole milk (8 ounces).

Treatment B: 1 tablet of metaxalone) with 240 mL of room temperature water without food. The study drug was administered with 240 mL room temperature water. A mouth check was performed to verify that the subjects swallowed the dose. Subjects were sequentially dosed at 1 minute intervals. The actual time of dosing was recorded on the Master Flow Sheet (refer to the Appendix 16.3.2 Clinical Study Data). Drug administration (1×400 mg capsule) was assisted with 240 mL of room temperature water consumed under direct observation. Immediately after administration of product, the subject's oral cavity was checked to confirm complete medication and fluid consumption. Dosing was completed as scheduled in 42 of 44 subjects.

The drug substance, metaxalone, was dosed in tablet form. Content: 400 mg; Route: Oral, Batch/Lot No.: SKLWW263F; Expiration Date: FEB03; Manufacturer: West-Ward Pharmaceutical Corp

All pharmacokinetic parameters were analyzed by non-compartmental methods. The following PK parameters were calculated for the two PK profiles and are defined as follows:

Tmax: Time to maximum concentration;

Cmax: Observed maximum concentration;

Kel: Slope of terminal linear portion of concentration/time curve;

T½: Half-life of metaxalone calculated as: 0.693/Kel;

AUC(last): Area under the curve to last quantifiable concentration as measured by the trapezoidal rule;

AUC(inf): The AUC value extrapolated to infinity calculated as: AUC(inf)=AUC(last)+C(t)last/Kel where C(t) last is the last measurable concentration.

Statistical Analysis

All statistical analyses were performed using SAS® software version 6.08 or higher. The PK parameters between the two treatments were compared using an appropriate ANOVA model (analysis of variance) that includes term for treatment, sequence, and period effect. Ninety percent confidence interval was computed for the Cmax and AUC values of the fed treatment with fasting as the reference treatment. During the study there were no protocol deviations to confound the pharmacokinetic and bioavailability analyses. Study results were not corrected for drug potency. The individual test results are summarized in table I

TABLE I

Summary of AUC_{inf} and Ln-Transformed AUC_{inf} for Skelaxin ® Administered With Food (A) vs. Skelaxin ® Administered Without Food (B)

Subj	Seq.	A: With Food (ng/mL)	B: Without Food (ng/mL)	(A − B)	Ratio (A/B)	% Ratio (A/B) *100	Log_e A Ln(A)	Log_e B Ln(B)	Log_e Ratio Ln (Ratio)
2	1	9031	9855	824	0.916	91.64	9.108	9.196	0.087
3	2	9809	13103	3494	0.733	73.33	9.170	9.481	0.310
4	2	5011	3867	1144	1.296	129.58	8.519	8.260	0.259
5	1	3589	2530	859	1.340	133.95	8.128	7.836	0.292
6	2	10456	7302	3154	1.432	143.19	9.255	8.896	0.359
7	2	11217	11103	114	1.010	101.03	9.325	9.315	0.010
8	2	4025	3857	168	1.044	104.36	8.300	8.258	0.043
9	2	13708	8876	4832	1.544	154.44	9.526	9.091	0.435
11	2	8122	6570	1552	1.236	123.62	9.002	8.790	0.212
12	1	6739	5470	1269	1.232	123.20	8.816	8.607	0.209
13	2	4614	4360	254	1.058	105.83	8.437	8.380	0.057
14	1	17347	13467	3880	1.288	128.81	9.761	9.508	0.253
15	2	5488	3535	1953	1.552	155.25	8.610	8.170	0.440
16	1	12327	12025	302	1.025	102.51	9.420	9.395	0.025
17	1	4070	3320	750	1.226	122.59	8.311	8.108	0.204
18	1	5296	4365	931	1.213	121.33	8.575	8.381	0.193
19	2	8022	8271	249	0.970	96.99	8.990	9.021	0.031
20	2	2962	2874	88	1.031	103.06	7.994	7.963	0.030
21	1	9143	7173	1970	1.275	127.46	9.123	8.878	0.243
22	2	11873	7742	4131	1.534	153.36	9.382	8.954	0.428
23	1	10456	9983	473	1.047	104.74	9.255	9.209	0.046
24	1	6507	5529	978	1.177	117.69	8.781	8.618	0.163
25	2	12145	10272	1871	1.182	118.21	9.405	9.237	0.167
26	1	4519	5391	872	0.838	83.82	8.416	8.593	0.176

TABLE I-continued

Summary of AUC_{inf} and Ln-Transformed AUC_{inf} for Skelaxin ® Administered With Food (A) vs. Skelaxin ® Administered Without Food (B)

Subj	Seq.	A: With Food (ng/mL)	B: Without Food (ng/mL)	(A − B)	Ratio (A/B)	% Ratio (A/B) *100	Log, A Ln(A)	Log, B Ln(B)	Log, Ratio Ln (Ratio)
27	1	5208	5061	147	1.029	102.90	8.558	8.529	0.029
28	2	5197	5032	185	1.037	103.69	8.556	8.520	0.036
29	1	10355	11601	1246	0.893	89.26	9.245	9.359	0.114
30	1	7350	6452	898	1.139	113.92	8.902	8.772	0.130
31	1	7899	7677	222	1.029	102.89	8.974	8.946	0.029
32	2	6719	4440	2279	1.513	151.33	8.813	8.398	0.414
33	2	11295	11316	21	0.998	99.81	9.332	9.334	0.002
34	2	13357	13580	223	0.984	98.36	9.500	9.516	0.017
35	2	10710	10138	572	1.056	105.64	9.279	9.224	0.055
36	1	19077	19329	252	0.987	98.70	9.856	9.869	0.013
37	1	6727	4454	2273	1.510	151.03	8.814	8.402	0.412
38	2	19024	9934	9090	1.915	191.50	9.853	9.204	0.650
39	1	3060	3284	224	0.932	93.18	8.026	8.097	0.071
40	1	5188	4203	985	1.234	123.44	8.554	8.344	0.211
41	1	7273	6574	699	1.106	110.63	8.892	8.791	0.101
42	2	3958	3642	316	1.087	108.68	8.283	8.200	0.083
43	1	8837	4642	4195	1.904	190.37	9.087	8.443	0.644
44	2	11427	11935	508	0.957	95.74	9.344	9.387	0.043

Differences were declared to be significant at the 5% level. The ratio of the geometric means for the ln-transformed data and the corresponding 90% confidence intervals were calculated for AUC(last), AUC(inf), and Cmax. The calculations for the confidence intervals used the least squares means (LSMEANS) and the standard error of the estimate, both generated by the SAS® software.

The lower limit of quantitation for metaxalone was 10 ng/mL. For statistical analysis, subject sample values below the lower limit of quantitation were reported as zero.

Tables IIa and IIb summarize the results of the analyses performed on the pharmacokinetic parameters obtained from the fed and fasted states.

TABLE IIa

	Ln-Transformed	Ln-Transformed	Ln-Transformed
Metaxalone Treatment A Geometric Mean	AUC(last) 7523.00	AUCinf 7630.53	Cmax 1536.23
Treatment B Geometric Mean	6094.12	6615.24	865.34
% Ratio	123.48	115.35	177.53
90% Confidence Interval	(116.40, 130.99)	(109.24, 121.80)	(156.62, 201.23)

TABLE IIb

Metaxalone	AUC(last)	AUCinf	Cmax	Tmax	T1/2
Treatment A Least Squares Mean	9439.62	8541.31	1773.61	4.39	2.37
Treatment B Least Squares Mean	6861.81	7478.80	983.37	3.32	9.04

With a 5% significance level, the ANOVA detected statistically significant differences between treatments for ln-transformed AUC(last), AUCinf, and Cmax, as well as for untransformed AUC(last), AUC(inf), Cmax, Tmax, T½, and Kel. The ANOVA detected no statistically significant differences between periods or between sequences.

The mean $T_{1/2}$ (half-life) of metaxalone with food and without food were 2.37 and 9.04 hours respectively. The exact reason for this discrepancy is unclear. However, the AUC last is outside the confidence interval, indicating a significant food effect.

Ratio (A/B) of least-squares means for AUC(last), AUC (inf) and Cmax were 123.48%, 115.35% and 177.53%, respectively demonstrating that metaxalone administered with food increased both its rate and extent of absorption.

ANOVA detected statistically significant differences between treatments for ln-transformed AUC(last), AUC (inf), and Cmax, as well as for untransformed AUC(last), AUC(inf),Cmax, T½, and Kel. ANOVA did not detect any statistically significant differences between treatments for untransformed Tmax.

Conclusion: Administration with food increases both the rate and extent of absorption of metaxalone 400 mg tablets when administered as a single dose. The bioavailability of metaxalone 400 mg tablets increased when administrated with food.

Article of Manufacture

The article of manufacture comprises a container holding an immediate release pharmaceutical composition suitable for oral administration of metaxalone in combination with printed labeling instructions providing a discussion of when a particular dosage form should be administered with food and when it should be taken on an empty stomach. The composition will be contained in any suitable container capable of holding and dispensing the dosage form and which will not significantly interact with the composition and will further be in physical relation with the appropriate labeling advising that an immediate release tablet dosage form has less somnolence associated with its use if taken on an empty stomach and an immediate release multiparticulate dosage form has less somnolence associated with its use if taken with food. The labeling instructions will be consistent with the methods of treatment as described hereinbefore.

The labeling may be associated with the container by any means that maintain a physical proximity of the two, by way of non-limiting example, they may both be contained in a packaging material such as a box or plastic shrink wrap or may be associated with the instructions being bonded to the container such as with glue that does not obscure the labeling instructions or other bonding or holding means.

While the invention has been described by discussion of embodiments of the invention and non-limiting examples thereof, one of ordinary skill in the art may, upon reading the specification and claims, envision other embodiments and variations which are also within the intended scope of the invention and therefore the scope of the invention shall only be construed and defined by the scope of the appended claims.

We claim:

1. A method of increasing the oral bioavailability of metaxalone to a patient receiving metaxalone therapy comprising administering to the patient a therapeutically effective amount of metaxalone in a pharmaceutical composition with food.

2. The method of claim 1 wherein the therapeutically effective amount is 200 mg to 900 mg.

3. The method of claim 1 wherein the therapeutically effective amount is 400 mg to 800 mg.

4. The method of claim 1 wherein the administration to the patient occurs between 30 minutes prior to 2 hours after consuming food.

5. The method of claim 1 wherein the administration to the patient is substantially at the same time as the consumption of the food.

6. The method of claim 1 wherein the administration to the patient is immediately after the consumption of food up to 1 hour after said consumption.

7. The method of claim 1 wherein the pharmaceutical composition comprises a tablet.

8. The method of claim 7 wherein the tablet is in unit dosage form.

9. A method of increasing the rate and extent of absorption of an oral dosage form of metaxalone as measured by the drug concentration attained in the blood stream over time in a patient in need of a therapeutic effect thereof comprising, administering to the patient a therapeutically effective amount of metaxalone in a pharmaceutical composition with food.

10. The method of claim 9 wherein the therapeutically effective amount is about 200 mg to about 900 mg.

11. The method of claim 9 wherein the therapeutically effective amount is from about 400 mg to about 800 mg.

12. The method of claim 9 wherein the administration to the patient occurs between about 30 minutes prior to about 2 hours after consuming food.

13. The method of claim 9 wherein the administration to the patient is substantially at the same time as the consumption of the food.

14. The method of claim 9 wherein the administration to the patient is immediately after the consumption of food up to about one hour after said consumption.

15. The method of claim 9 wherein the pharmaceutical composition comprises a tablet.

16. The method of claim 15 wherein the pharmaceutical composition comprises a unit dosage form.

17. A method of increasing the oral bioavailability of metaxalone to a patient receiving metaxalone therapy comprising administering to the patient a pharmaceutical tablet comprising 400 mg to 800 mg of metaxalone, with food, wherein the administration results in an increase in the maximal plasma concentration (Cmax) and extent of absorption (AUC(last)) of metaxalone compared to administration without food.

18. The method of claim 17 wherein the administration to the patient occurs between 30 minutes prior to 2 hours after consuming food.

19. The method of claim 17 wherein the administration to the patient is substantially at the same time as the consumption of the food.

20. The method of claim 17 wherein the administration to the patient is immediately after the consumption of food up to 1 hour after said consumption.

21. The method of claim 1, further comprising informing the patient that the administration of a therapeutically effective amount of metaxalone in a pharmaceutical composition with food results in an increase in the maximal plasma concentration (Cmax) and extent of absorption (AUC(last)) of metaxalone compared to administration without food.

22. The method of claim 1, wherein the metaxalone is from a container with printed labeling advising that administration with food results in an increase in the maximal plasma concentration (Cmax) and extent of absorption (AUC(last)) of metaxalone compared to administration without food.

* * * * *

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 6,407,128 B1
DATED : June 18, 2002
INVENTOR(S) : Scalfe et al.

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Column 1,
Line 38, before "Nov." insert open parenthesis -- (Nov. --;

Column 2,
Line 67, "th e" should read -- the --;

Column 5,
Line 29, "in-transformed" should read -- 1n-transformed --,
Line 66, "in-transformed" should read -- 1n-transformed --; and

Column 6,
Line 40, "In-transformed" should read -- 1n-transformed --.

Signed and Sealed this

Twenty-third Day of July, 2002

Attest:

Attesting Officer

JAMES E. ROGAN
Director of the United States Patent and Trademark Office

EXHIBIT 2

US006683102B2

(12) **United States Patent**
Scaife et al.

(10) **Patent No.: US 6,683,102 B2**
(45) **Date of Patent: Jan. 27, 2004**

(54) **METHODS OF USING METAXALONE IN THE TREATMENT OF MUSCULOSKELETAL CONDITIONS**

(76) Inventors: **Michael Scaife**, 13460 Old Winery Rd., Poway, CA (US) 92064; **Jaymin Shah**, 1092 Dalles Ave., Sunnyvale, CA (US) 94086

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

(21) Appl. No.: **10/104,044**

(22) Filed: **Mar. 25, 2002**

(65) **Prior Publication Data**

US 2003/0216457 A1 Nov. 20, 2003

Related U.S. Application Data

(63) Continuation of application No. 09/998,206, filed on Dec. 3, 2001, now Pat. No. 6,407,128.

(51) **Int. Cl.**[7] **A61K 31/42**
(52) **U.S. Cl.** **514/376**
(58) **Field of Search** 514/376

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Primary Examiner—Raymond Henley, III

(57) **ABSTRACT**

A method of increasing the bioavailability of metaxalone by administration of an oral dosage form with food is provided, as well as an article of manufacture comprising an oral dosage form of metaxalone in a suitable container and associated with printed labeling which describes the increased bioavailability of the medication in the container when taken with food.

15 Claims, 1 Drawing Sheet

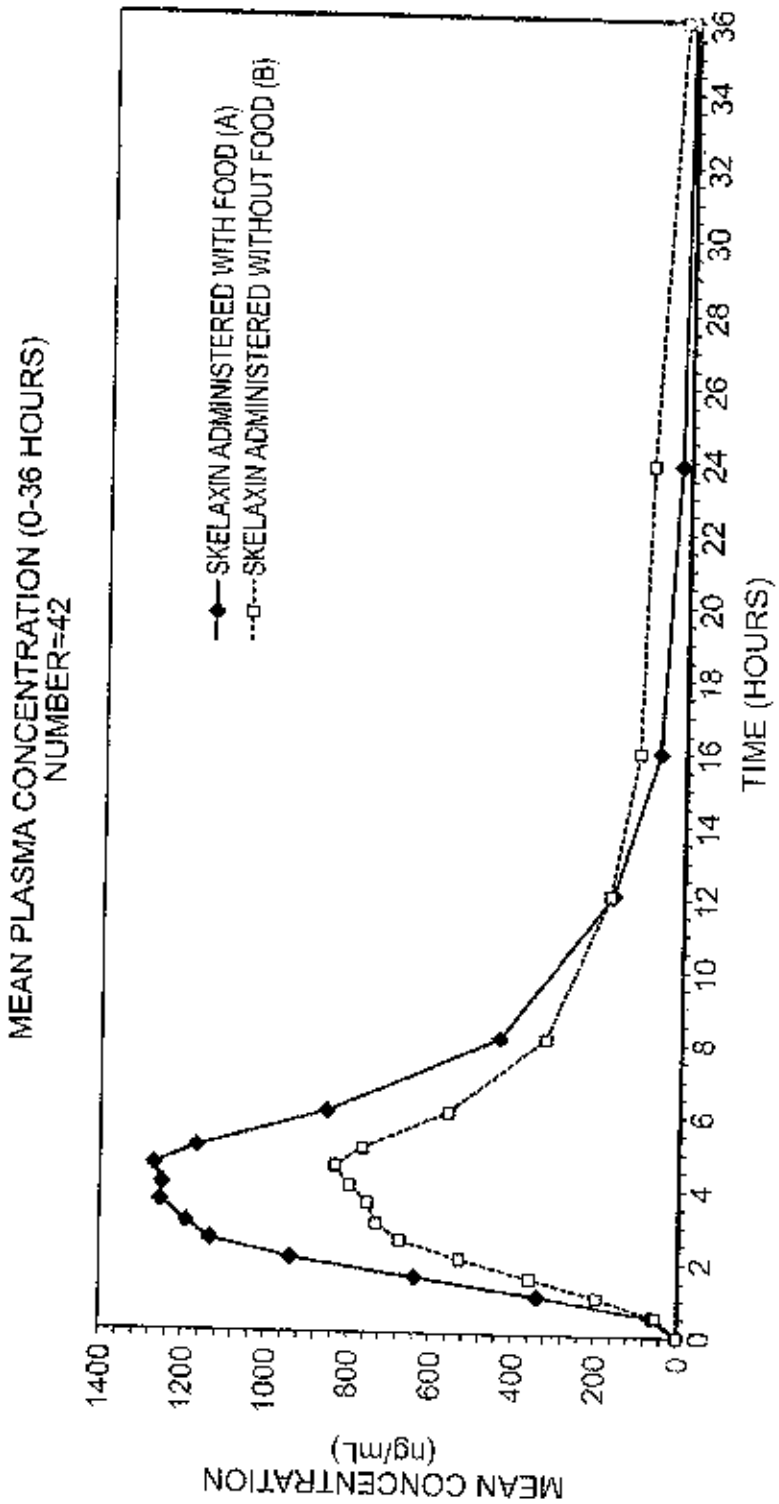
MEAN PLASMA CONCENTRATION (0-36 HOURS)
NUMBER=42
SKELAXIN ADMINISTERED WITH FOOD (A)
SKELAXIN ADMINISTERED WITHOUT FOOD (B)
MEAN CONCENTRATION
(ng/mL)
TIME (HOURS)
0
200
400
600
800
1000
1200
1400
0
2
4
6
8
10
12
14
16
18
20
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FIG. 1

METHODS OF USING METAXALONE IN THE TREATMENT OF MUSCULOSKELETAL CONDITIONS

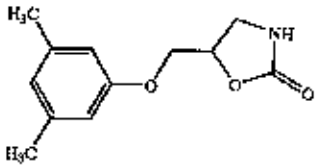
This is a continuation of application Ser. No. 09/998,206, filed Dec. 3, 2001, now U.S. Pat. No. 6,407,128, the disclosure of which is incorporated herein by reference.

FIELD OF THE INVENTION

The invention relates to methods for increasing the bioavailability of a medicinal agent, namely metaxalone (5-[(3,5-dimethylphenoxy)methyl]-2 oxazolidinone).

BACKGROUND OF THE INVENTION

Metaxalone (Skelaxin®) has the following chemical structure and name:



5-[(3,5-dimethylphenoxy)methyl]-2 oxazolidinone

Skelaxin is indicated as an adjunct to rest, physical therapy, and other measures for the relief of discomforts associated with acute, painful musculoskeletal conditions. The mode of action of this drug has not been clearly identified, but may be related to its sedative properties. Metaxalone does not directly relax tense skeletal muscles in man. The commercially available tablet contains: metaxalone, 400 mg along with inert compression tableting excipients.

Metaxalone is further described at Monograph no. 5838 of the Merck Index (Eleventh Addition, Merck & Co., 1989) and is also identified by CAS Registry Number: 1665-48-1. It is also known by the drug code, AHR-438; and the drug product containing it is marketed as Skelaxin® (a trademark of Elan Pharmaceuticals, Inc.).

Preparation of metaxalone is described in Lunsford et al., J. Am. Chem. Soc. 82, 1166 (1960) and U.S. Pat. No. 3,062,827 to Lunsford (Nov. 6, 1962 Assignee A. H. Robins), which is incorporated herein in its entirety by reference. The '827 patent discloses the compound and related species as anticonvulsants and antispasmodics, however, these activities have not been borne out by clinical experience.

Metaxalone is a central nervous system depressant that has sedative and skeletal muscle relaxant effects. Metaxalone is indicated as an adjunct to rest, physical therapy and other measures for the relief of discomforts associated with acute, painful muscoloskeletal conditions. See Skelaxin® monograph, 2001 Physicians' Desk Reference®, Medical Economics Company, Inc. (publisher) Montvale, N.J.

The most frequent reactions to metaxalone include nausea, vomiting, gastrointestinal upset, drowsiness, dizziness, headache, and nervousness or "irritability." Other adverse reactions are: hypersensitivity reaction, characterized by a light rash with or without pruritus; leukopenia; hemolytic anemia; jaundice.

Pharmacokinetic studies have not previously been conducted to date to evaluate the effect of food on the pharmacokinetics of metaxalone. The hydrophobicity of the metaxalone molecule and the dosage amount required for a therapeutic effect both point to probably limited absorption from the gut when administered orally. More oral bioavailability of the drug substance has been sought to increase both speed of onset and amount of therapeutic effect.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 is a plot of the mean plasma concentration of metaxalone in nanograms per milliliter versus the time elapsed from administration of the dosage form. Two (2) plots are shown for the 400 mg dosage form administered with and without food.

SUMMARY OF THE INVENTION

The subject of this invention is the unexpected finding that administration of metaxalone with food increases both the rate and extent of absorption via the oral dosage form in human subjects.

One aspect of this invention is a method of increasing the bioavailability of metaxalone in a human patient receiving metaxalone therapy wherein the metaxalone is contained in a pharmaceutical composition, which method comprises administering a therapeutically effective amount of metaxalone to the patient with food.

Another aspect of the invention is providing a method of increasing rate and extent of metaxalone absorption as measured by the drug concentration attained in the blood stream over time of a patient receiving, the drug in an oral dosage form which method comprises administering a therapeutically effective amount of metaxalone to the patient with food.

Preferably the therapeutic amount is between about 200 mg to about 900 mg, and more preferably between about 400 mg to about 800 mg. Unit dosage forms are preferred.

Preferably the food is a solid food with sufficient bulk and fat content that it is not rapidly dissolved and absorbed in the stomach. More preferably the food is a meal, such as breakfast, lunch or dinner. Advantageously the dosage is administered to the patient between about 30 minutes prior to about 2 hours after eating a meal, most advantageously the dosage is administered within 15 minutes of eating a meal. The terms "without food", "fasted" and "an empty stomach" are defined to mean the condition of not having consumed solid food for about 1 hour prior to until about 2 hours after such consumption.

Yet another aspect of this invention is providing information to prescribing physicians and patients receiving metaxalone therapy useful in maximizing the therapeutic effect of the oral dosage form, by recommending that metaxalone be taken within about half an hour of consuming food.

Another aspect of this invention is an article of manufacture that comprises a container containing a pharmaceutical composition comprising metaxalone wherein the container holds preferably the metaxalone composition in unit dosage form and is associated with printed labeling instructions advising of the differing absorption when the pharmaceutical composition is taken with and without food.

The effect of food on metaxalone absorption was identified in a study designed to compare the bioavailability of 400 mg of metaxalone in the formulation the drug product Skelaxin® administered to healthy volunteers with and without food.

An objective was to evaluate the bioavailability of metaxalone when administered to subjects with and without food. A single center, single dose, open-label, two-period,

randomized, crossover trial in healthy subjects was conducted over a period of approximately 32 days.

The two study drug treatments were as follows:

Treatment A: metaxalone tablet (400 mg) administered with food

Treatment B: metaxalone tablet (400 mg) administered without food

In fed treatment condition A, study drug was taken 15 minutes after the test meal. The test meal was consumed over a 15 minute time period. There was a 6-day washout period between study drug administrations. Seventeen blood samples were collected, starting with baseline (0 hour) and at the following time points: 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 6, 8, 12, 16, 24, and 36 hours.

A total of 44 subjects (31 males/13 females) were enrolled and dosed. Only the plasma of subjects who completed the study were assayed and used for the pharmacokinetic analysis.

A single center, single dose, open label, two-period crossover trial was devised for study in healthy subjects. Each administration was a single oral dose of one Skelaxin® 400 mg tablet with or without food. The study drug was administered as follows:

Treatment A: One (1) 400 mg tablet of metaxalone with 240 mL of room temperature water with food: Breakfast was given to the subjects 30 minutes prior to dosing and eaten within a 15 minute period. The dose of study drug was administered to the subjects 15 minutes after the breakfast was finished.

The breakfast consisted of the following:

2 eggs (fried in butter);

2 strips of bacon;

2 slices of toast with butter;

4 ounces of hash brown potatoes;

1 glass whole milk (8 ounces).

Treatment B: 1 tablet of metaxalone) with 240 mL of room temperature water without food. The study drug was administered with 240 mL room temperature water. A mouth check was performed to verify that the subjects swallowed the dose. Subjects were sequentially dosed at 1 minute intervals. The actual time of dosing was recorded on the Master Flow Sheet (refer to the Appendix 16.3.2 Clinical Study Data). Drug administration (1×400 mg capsule) was assisted with 240 mL of room temperature water consumed under direct observation. Immediately after administration of product, the subject's oral cavity was checked to confirm complete medication and fluid consumption. Dosing was completed as scheduled in 42 of 44 subjects.

The drug substance, metaxalone; was dosed in tablet form.

Content: 400 mg; Route: Oral, Batch/Lot No.: SKLWW263F;

Expiration Date: February 03; Manufacturer: West-Ward Pharmaceutical Corp

All pharmacokinetic parameters were analyzed by non-compartmental methods. The following PK parameters were calculated for the two PK profiles and are defined as follows:

Tmax: Time to maximum concentration;

Cmax: Observed maximum concentration;

kel: Slope of terminal linear portion of concentration/time curve;

T½: Half-life of metaxalone calculated as: 0.693/Kel;

AUC(last): Area under the curve to last quantifiable concentration as measured by the trapezoidal rule;

AUC(inf): The AUC value extrapolated to infinity calculated as: AUC(inf)=AUC(last)+C(t)last/Kel where C(t) last is the last measurable concentration.

Statistical Analysis

All statistical analyses were performed using SAS® software version 6.08 or higher. The PK parameters between the two treatments were compared using an appropriate ANOVA model (analysis of variance) that includes term for treatment, sequence, and period effect. Ninety percent confidence interval was computed for the Cmax and AUC values of the fed treatment with fasting as the reference treatment. During the study there were no protocol deviations to confound the pharmacokinetic and bioavailability analyses. Study results were not corrected for drug potency. The individual test results are summarized in table I

TABLE I

Summary of AUC_{inf} and Ln-Transformed AUC_{inf} for Skelaxin ® Administered With Food (A) vs. Skelaxin ® Administered Without Food (B)

Subj	Seq.	A:With Food (ng/mL)	B:Without Food (ng/mL)	(A − B)	Ratio (A/B)	% Ratio (A/B) *100	Log_e A Ln(A)	Log_e B Ln(B)	Log_e Ratio Ln (Ratio)
2	1	9031	9855	824	0.916	91.64	9.108	9.196	0.087
3	2	9609	13103	3494	0.733	73.33	9.170	9.481	0.310
4	2	5011	3867	1144	1.296	129.58	8.519	8.260	0.259
5	1	3389	2530	859	1.340	133.95	8.128	7.836	0.292
6	2	10456	7302	3154	1.432	143.19	9.255	8.896	0.359
7	2	11217	11103	114	1.010	101.03	9.325	9.315	0.010
8	2	4025	3857	169	1.044	104.36	8.300	8.258	0.043
9	2	13708	8876	4832	1.544	154.44	9.526	9.091	0.435
11	2	8122	6570	1552	1.236	123.62	9.002	8.790	0.212
12	1	5739	5470	1269	1.232	123.20	8.816	8.607	0.209
13	2	4614	4360	254	1.058	105.83	8.437	8.380	0.057
14	1	17347	13467	3880	1.288	128.81	9.761	9.508	0.253
15	3	5488	3535	1953	1.552	155.25	8.610	8.170	0.440
16	1	12327	12025	302	1.025	102.51	9.420	9.395	0.025
17	1	4070	3320	750	1.226	122.59	8.311	8.108	0.204
18	1	5296	4365	931	1.213	121.33	8.575	8.381	0.193
19	2	8022	8271	249	0.970	96.99	8.990	9.021	0.031
20	2	2962	2874	88	1.031	103.06	7.994	7.963	0.030
21	1	9143	7173	1970	1.275	127.46	9.121	8.878	0.243

TABLE I-continued

Summary of AUC_{inf} and Ln-Transformed AUC_{inf} for Skelaxin ® Administered With Food (A) vs. Skelaxin ® Administered Without Food (B)

Subj	Seq.	A:With Food (ng/mL)	B:Without Food (ng/mL)	(A – B)	Ratio (A/B)	% Ratio (A/B) *100	Log, A Ln(A)	Log, B Ln(B)	Log, Ratio Ln (Ratio)
22	2	11873	7742	4131	1.534	153.36	9.382	8.954	0.428
23	1	10456	9983	473	1.047	104.74	9.255	9.209	0.046
24	1	6507	5529	978	1.177	117.69	8.781	8.618	0.163
25	2	12143	10272	1871	1.182	118.21	9.405	9.237	0.167
26	1	4519	5391	872	0.838	83.82	8.416	8.592	0.176
27	1	5208	5061	147	1.029	102.90	8.558	8.529	0.029
28	2	5197	5012	185	1.037	103.69	8.556	8.520	0.036
29	1	10355	11601	1246	0.893	89.26	9.245	9.359	0.114
30	1	7350	6452	898	1.139	113.92	8.902	8.772	0.130
31	1	7899	7677	222	1.029	102.89	8.974	8.946	0.029
32	2	6729	4440	2289	1.513	151.53	8.813	8.398	0.414
33	2	11295	11316	21	0.998	99.83	9.332	9.334	0.002
34	2	13357	13580	223	0.984	98.36	9.500	9.516	0.017
35	2	10710	10138	572	1.056	105.64	9.279	9.224	0.055
36	1	19077	19329	252	0.987	98.70	9.856	9.869	0.013
37	1	6727	4454	2273	1.510	151.03	8.814	8.402	0.412
38	2	19024	9934	9090	1.915	191.50	9.853	9.204	0.650
39	1	3060	3284	224	0.932	93.18	8.026	8.097	0.071
40	1	5188	4203	985	1.234	123.44	8.554	8.344	0.211
41	1	7273	6574	699	1.106	110.63	8.892	8.791	0.101
42	2	3958	3642	316	1.087	108.68	8.283	8.200	0.083
43	1	8837	4642	4195	1.904	190.37	9.087	8.443	0.644
44	2	11427	11935	508	0.957	95.74	9.344	9.387	0.043

Differences were declared to be significant at the 5% level. The ratio of the geometric means for the ln-transformed data and the corresponding 90% confidence intervals were calculated for AUC(last), AUC(inf), and Cmax. The calculations for the confidence intervals used the least squares means (LSMEANS) and the standard error of the estimate, both generated by the SAS® software.

The lower limit of quantitation for metaxalone was 10 ng/mL. For statistical analysis, subject sample values below the lower limit of quantitation were reported as zero.

Tables IIa and IIb summarize the results of the analyses performed on the pharmacokinetic parameters obtained from the fed and fasted states.

TABLE IIa

Metaxalone	AUC (last)	AUCinf	Cmax
Treatment A Geometric Mean	7525.00	7630.53	1536.23
Treatment B Geometric Mean	6094.12	665.24	865.34
% Ratio	123.48	115.35	177.53
90% Confidence Interval	(116.40, 130.99)	(109.24, 121.80)	(156.62, 201.23)

TABLE IIb

Metaxalone	AUC (last)	AUCinf	Cmax	Tmax	T1/2
Treatment A Least Squares Mean	8439.62	8541.31	1775.61	4.29	2.37
Treatment B Least Squares Mean	6961.81	7478.99	983.37	3.32	9.04

With a 5% significance level, the ANOVA detected statistically significant differences between treatments for ln-transformed AUC(last), AUCinf, and Cmax, as well as for untransformed AUC(last), AUC(inf), Cmax, Tmax, T½, and Kel. The ANOVA detected no statistically significant differences between periods or between sequences.

The mean $T_{1/2}$ (half-life) of metaxalone with food and without food were 2.37 and 9.04 hours respectively. The exact reason for this discrepancy is unclear. However, the AUC last is outside the confidence interval, indicating a significant food effect.

Ratio (A/B) of geometric means for AUC(last), AUC(inf) and Cmax were 123.48%, 115.35% and 177.53%, respectively demonstrating that metaxalone administered with food increased both its rate and extent of absorption.

ANOVA detected statistically significant differences between treatments for ln-transformed AUC(last), AUC (inf), and Cmax, as well as for untransformed AUC(last), AUC(inf),Cmax, T½, and Kel. ANOVA did not detect any statistically significant differences between treatments for untransformed Tmax.

Conclusion: Administration with food increases both the rate and extent of absorption of metaxalone 400 mg tablets when administered as a single dose. The bioavailability of metaxalone 400 mg tablets increased when administrated with food.

Article of Manufacture

The article of manufacture comprises a container holding an immediate release pharmaceutical composition suitable for oral administration of metaxalone in combination with printed labeling instructions providing a discussion of when a particular dosage form should be administered with food and when it should be taken on an empty stomach. The composition will be contained in any suitable container capable of holding and dispensing the dosage form and which will not significantly interact with the composition and will further be in physical relation with the appropriate labeling advising that an immediate release tablet dosage form has less somnolence associated with its use if taken on an empty stomach and an immediate release multiparticulate

dosage form has less somnolence associated with its use if taken with food. The labeling instructions will be consistent with the methods of treatment as described hereinbefore. The labeling may be associated with the container by any means that maintain a physical proximity of the two, by way of non-limiting example, they may both be contained in a packaging material such as a box or plastic shrink wrap or may be associated with the instructions being bonded to the container such as with glue that does not obscure the labeling instructions or other bonding or holding means.

While the invention has been described by discussion of embodiments of the invention and non-limiting examples thereof, one of ordinary skill in the art may, upon reading the specification and claims, envision other embodiments and variations which are also within the intended scope of the invention and therefore the scope of the invention shall only be construed and defined by the scope of the appended claims.

We claim:

1. A method of using metaxalone in the treatment of musculoskeletal conditions comprising:

providing the patient with a therapeutically effective amount of metaxalone; and

informing the patient that the administration of metaxalone with food results in an increase in at least one of C(max) and AUC(last) of metaxalone compared to administration without food.

2. The method according to claim 1, wherein therapeutically effective amount of metaxalone comprises 200 mg to 900 mg of metaxalone.

3. The method according to claim 2, wherein the therapeutically effective amount of metaxalone comprises 400 mg to 800 mg of metaxalone.

4. The method according to claim 1, wherein the metaxalone is provided in tablet form.

5. The method according to claim 4, wherein the tablet is in unit dosage form.

6. A method of using metaxalone in the treatment of musculoskeletal conditions comprising:

informing a patient with musculoskeletal conditions that the administration of a therapeutically effective amount of metaxalone with food results in an increase in at least one of C(max) and AUC(last) of metaxalone compared to administration without food.

7. A method of using metaxalone in the treatment of musculoskeletal conditions comprising altering the oral bioavailability of metaxalone by:

obtaining metaxalone from a container providing information that administration of metaxalone with food increases at least one of C(max) and AUC(last) of metaxalone compared to administration without food, and

ingesting the metaxalone with food.

8. A method of using metaxalone in the treatment of musculoskeletal conditions comprising:

administering to a patient in need of treatment a therapeutically effective amount of metaxalone, with food, wherein the administration of the metaxalone with food results in an increase in at least one of C(max) and AUC(last) of metaxalone as compared to administration of metaxalone in a fasted state; and

informing the patient that the administration of a therapeutically effective amount of metaxalone in a pharmaceutical composition with food results in an increase in at least one of C(max) and AUC(last) of metaxalone compared to administration in a fasted state.

9. The method according to claim 8, wherein the metaxalone is from a container with printed labeling advising that administration with food results in an increase in at least one of C(max) and AUC(last) of metaxalone compared to administration in a fasted state.

10. The method according to claim 9, wherein the metaxalone is provided in tablet form.

11. The method according to claim 10, wherein the metaxalone is provided in 400 mg tablet form.

12. The method according to claim 9, wherein the printed labeling advises that the administration of the metaxalone with food results in an increase in the C(max) of 177.5%.

13. The method according to claim 9, wherein the printed labeling advises that the administration of the metaxalone with food results in an increase in the AUC(last) of 123.5%.

14. The method according to claim 9, wherein the printed labeling further advises that the administration of the metaxalone with food results in an increase in AUC(inf) of 115.4%.

15. The method according to claim 8, wherein the metaxalone is provided in 400 mg tablet form, and the printed labeling advises that administration of metaxalone with food results in an increase in C(max), AUC(last), and AUC(inf), of 177.5%, 123.5%, and 115.4%, respectively, compared to administration of metaxalone in a fasted state.

* * * * *

EXHIBIT 3

Proprietary Name Search Results from "OB_Rx" table for query on "skelaxin."

Appl No	TE Code	RLD	Active Ingredient	Dosage Form; Route	Strength	Proprietary Name	Applicant
013217		No	METAXALONE	TABLET; ORAL	400MG	SKELAXIN	JONES PHARMA INC
013217		Yes	METAXALONE	TABLET; ORAL	800MG	SKELAXIN	JONES PHARMA INC

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FDA/Center for Drug Evaluation and Research
Office of Generic Drugs
Division of Labeling and Program Support
Update Frequency:

Orange Book Data - **Monthly**

Orange Book Data Updated Through September, 2004

Orange Book Patent Data Only - **Daily**

Patent Data Last Updated: December 14, 2004

Search results from the "OB_Rx" table for query on "013217."

Active Ingredient:	METAXALONE
Dosage Form;Route:	TABLET; ORAL
Proprietary Name:	SKELAXIN
Applicant:	JONES PHARMA INC
Strength:	400MG
Application Number:	013217
Product Number:	001
Approval Date:	Approved Prior to Jan 1, 1982
Reference Listed Drug	No
RX/OTC/DISCN:	RX
TE Code:	

Patent and Exclusivity Info for this product: View

Active Ingredient:	METAXALONE
Dosage Form;Route:	TABLET; ORAL
Proprietary Name:	SKELAXIN
Applicant:	JONES PHARMA INC
Strength:	800MG
Application Number:	013217
Product Number:	003
Approval Date:	Aug 30, 2002
Reference Listed Drug	Yes
RX/OTC/DISCN:	RX
TE Code:	

Patent and Exclusivity Info for this product: View

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Patent Data Last Updated: December 14, 2004

Patent and Exclusivity Search Results from query on Appl No 013217 Product 001 in the OB_Rx list.

Patent Data

Appl No	Prod No	Patent No	Patent Expiration	Drug Substance Claim	Drug Product Claim	Patent Use Code
013217	001	6407128	DEC 03,2021			U-189
013217	001	6683102	DEC 03,2021			U-189

Exclusivity Data

There is no unexpired exclusivity for this product.

Additional information:
1. Patents are published upon receipt by the Orange Book Staff and may not reflect the official receipt date as described in 21 CFR 314.53(d)(5).
2. Patents submitted on FDA Form 3542 and listed after August 18, 2003 will have one to three patent codes indicating specific patent claims as submitted by the sponsor and are detailed in the above table.
3. Patents listed prior to August 18, 2003 are flagged with method of use claims only as applicable and submitted by the sponsor. These patents may not be flagged with respect to other claims which may apply.
4. *PED and PED represent pediatric exclusivity. Patents with pediatric exclusivity granted after August 18, 2003 will be indicated with *PED as was done prior to August 18, 2003. Patents with *PED added after August 18, 2003 will not contain any information relative to the patent itself other than the *PED extension. Information related specifically to the patent will be conveyed on the original patent only.

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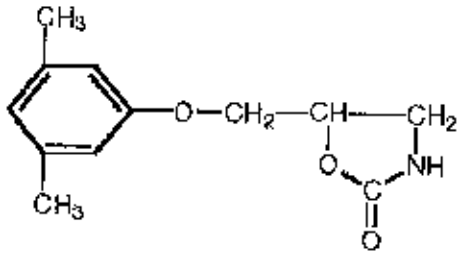
Patent Data Last Updated: December 14, 2004

EXHIBIT 4

SKELAXIN® (Metaxalone)

DESCRIPTION

SKELAXIN® (metaxalone) has the following chemical structure and name:



5-[(3,5-dimethylphenoxy) methyl]-2-oxazolidinone

SKELAXIN (metaxalone) is available as a 400 mg round, pale rose tablet and an 800 mg oval, pink scored tablet.

CLINICAL PHARMACOLOGY

The mechanism of action of metaxalone in humans has not been established, but may be due to general central nervous system depression. It has no direct action on the contractile mechanism of striated muscle, the motor end plate or the nerve fiber.

Pharmacokinetics: In a single center randomized, two-period crossover study in 42 healthy volunteers (31 males, 11 females), a single 400 mg SKELAXIN (metaxalone) tablet was administered under both fasted and fed conditions.

Under fasted conditions, mean peak plasma concentrations (C_{max}) of 865.3 ng/mL were achieved within 3.3 +/- 1.2 hours (S.D.) after dosing (T_{max}). Metaxalone concentrations declined with a mean terminal half-life ($t_{1/2}$) of 9.2 +/- 4.8 hours. The mean apparent oral clearance (CL/F) of metaxalone was 68 +/- 34 L/h.

In the same study, following a standardized high fat meal, food statistically significantly increased the rate (C_{max}) and extent of absorption ($AUC_{(0-t)}$, AUC_{inf}) of metaxalone from SKELAXIN tablets. Relative to the fasted treatment the observed increases were 177.5%, 123.5%, and 115.4%, respectively. The mean T_{max} was also increased to 4.3 +/- 2.3 hours, whereas the mean $t_{1/2}$ was decreased to 2.4 +/- 1.2 hours. This decrease in half-life over that seen in the fasted subjects is felt to be due to the more complete absorption of metaxalone in the presence of a meal resulting in a better estimate of half-life. The mean apparent oral clearance (CL/F) of metaxalone was relatively unchanged relative to fasted administration (59 +/- 29 L/hr). Although a higher C_{max} and AUC were observed

after the administration of SKELAXIN (metaxalone) with a standardized high fat meal, the clinical relevance of these effects is unknown.

In another single center, randomized four-period crossover study in 59 healthy volunteers (37 males, 22 females), the rate and extent of metaxalone absorption were determined after the administration of SKELAXIN tablets under both fasted and fed conditions. Under fasted conditions, the administration of two SKELAXIN 400 mg tablets produced peak plasma metaxalone concentrations (C_{max}) of 1653 ng/mL 3.0 $\pm$ 1.2 hours after dosing (T_{max}). Metaxalone concentrations declined with mean terminal half-life ($t_{½}$) of 8.0 $\pm$ 4.6 hours. The mean apparent oral clearance (CL/F) of metaxalone was 66 $\pm$ 34 L/hr. Except for a 17% decrease in mean C_{max}, these values were not statistically different from those after the administration of one SKELAXIN 800 mg tablet.

In the same study, the administration of two SKELAXIN 400 mg tablets following a standardized high fat meal showed an increase in the mean C_{max}, and the area under the curve ($AUC_{0\text{-}inf}$) of metaxalone by 194% and 142%, respectively. A high fat meal also increased the mean T_{max} to 4.9 +/- 2.3 hours but decreased the mean $t_{½}$ to 4.2 $\pm$ 2.5 hr. The effect of a high fat meal on the absorption of metaxalone from one SKELAXIN 800 mg tablet was very similar to that on the absorption from two SKELAXIN 400 mg tablets in quality and quantity. The clinical relevance of these effects is unknown.

The absolute bioavailability of metaxalone from SKELAXIN tablets is not known. Metaxalone is metabolized by the liver and excreted in the urine as unidentified metabolites. The impact of age, gender, hepatic, and renal disease on the pharmacokinetics of SKELAXIN (metaxalone) has not been determined. In the absence of such information, SKELAXIN should be used with caution in patients with hepatic and/or renal impairment and in the elderly.

INDICATIONS AND USAGE

SKELAXIN (metaxalone) is indicated as an adjunct to rest, physical therapy, and other measures for the relief of discomforts associated with acute, painful musculoskeletal conditions. The mode of action of this drug has not been clearly identified, but may be related to its sedative properties. Metaxalone does not directly relax tense skeletal muscles in man.

CONTRAINDICATIONS

Known hypersensitivity to any components of this product.
Known tendency to drug induced, hemolytic, or other anemias.
Significantly impaired renal or hepatic function.

WARNINGS

SKELAXIN may enhance the effects of alcohol and other CNS depressants.

PRECAUTIONS

Metaxalone should be administered with great care to patients with pre-existing liver damage. Serial

liver function studies should be performed in these patients.

False-positive Benedict's tests, due to an unknown reducing substance, have been noted. A glucose-specific test will differentiate findings.

Information for Patients
SKELAXIN may impair mental and/or physical abilities required for performance of hazardous tasks, such as operating machinery or driving a motor vehicle, especially when used with alcohol or other CNS depressants.

Drug Interactions
SKELAXIN may enhance the effects of alcohol, barbiturates and other CNS depressants.

Carcinogenesis, Mutagenesis, Impairment of Fertility
The carcinogenic potential of metaxalone has not been determined.

Pregnancy
Reproduction studies in rats have not revealed evidence of impaired fertility or harm to the fetus due to metaxalone. Post marketing experience has not revealed evidence of fetal injury, but such experience cannot exclude the possibility of infrequent or subtle damage to the human fetus. Safe use of metaxalone has not been established with regard to possible adverse effects upon fetal development. Therefore, metaxalone tablets should not be used in women who are or may become pregnant and particularly during early pregnancy unless in the judgement of the physician the potential benefits outweigh the possible hazards.

Nursing Mothers
It is not known whether this drug is secreted in human milk. As a general rule, nursing should not be undertaken while a patient is on a drug since many drugs are excreted in human milk.

Pediatric Use
Safety and effectiveness in children 12 years of age and below have not been established.

ADVERSE REACTIONS
The most frequent reactions to metaxalone include:
CNS: drowsiness, dizziness, headache, and nervousness or "irritability;"
Digestive: nausea, vomiting, gastrointestinal upset;
Immune system: hypersensitivity reaction, rash with or without pruritus;
Hematologic: leukopenia, hemolytic anemia;
Hepatobiliary: jaundice.
Though rare, anaphylactoid reactions have been reported with metaxalone.

OVERDOSAGE

Deaths by deliberate or accidental overdose have occurred with this class of drugs, particularly in combination with antidepressants and/or alcohol.

When determining the LD_{50} in rats and mice, progressive sedation, hypnosis and finally respiratory failure were noted as the dosage increased. In dogs, no LD_{50} could be determined as the higher doses produced an emetic action in 15 to 30 minutes.

Treatment - Gastric lavage and supportive therapy. Consultation with a regional poison control center is recommended.

DOSAGE AND ADMINISTRATION

The recommended dose for adults and children over 12 years of age is two 400 mg tablets (800 mg) or one 800 mg tablet three to four times a day.

HOW SUPPLIED

SKELAXIN (metaxalone) is available as a 400 mg pale rose tablet, inscribed with 8662 on the scored side and "C" on the other. Available in bottles of 100 (NDC 0086-0062-10) and in bottles of 500 (NDC 0086-0062-50).

SKELAXIN (metaxalone) is also available as an 800 mg oval, scored pink tablet inscribed with 8667 on the scored side and "S" on the other. Available in bottles of 100 (NDC 59075-068-10) and in bottles of 500 (NDC 59075-068-50).

Store at Controlled Room Temperature, between 15° C and 30° C (59° F and 86° F).

Rx Only

Revised: August, 2002

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/s/

Lawrence Goldkind
8/30/02 04:27:00 PM